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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,643	02/10/2005	Hideki Garren	022259-001010US	1611

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,643	GARREN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/06, 5/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment filed July 16, 2007 is acknowledged and has been entered. Claim 7 has been amended. New claims 25-30 have been added. Claims 1-30 are now pending in the instant application.

2. Applicant's election with traverse of Group I, claims 7-10 and 25-30, in the reply filed on July 16, 2007 is acknowledged. The traversal is on the ground(s) that the claims do indeed share a common technical feature that defines over the prior art. Applicants have asserted that Krieg et al 1995 does not teach a hexamer motif as presently claimed. Applicants have asserted that the oligonucleotides in Krieg et al 1995 are immunostimulatory nucleic acid sequences, not immune modulatory. This is not found persuasive because Krieg et al 1995 does disclose the claimed nucleic acid comprising a hexamer region as claimed. Table 13Md discloses the claimed hexamer region. With regard to the teaching of immune modulatory, it is noted that immune modulatory broadly encompasses both stimulation and suppression of immune responses.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-6 and 11-24 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 16, 2007.

4. The use of trademarks has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

5. Claims 7-10 and 25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a nucleic acid composition comprising a nucleic acid vector having a IMS that is a 22-mer having the CpG motif as described in claim 7, for example, does not reasonably provide enablement for a composition comprising a nucleic acid composition comprising a nucleic acid vector having a IMS that is a hexamer, having the CpG motif of the formulas set forth in claim 7, for example. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims (independent claim 7) is directed to a nucleic acid composition comprising: a nucleic acid vector having at least one cytosine to non-cytosine substitution within a CpG motif, wherein the CpG motif is of the formula 5'-purine-pyrimidine-C-G- pyrimidine-pyrimidine-3' or 5'-purine-purine-C-G-pyrimidine-pyrimidine-3', and wherein the cytosine to non-cytosine substitution is within the CpG dinucleotide.

A review of the specification discloses a 22-mer found in Example 1 that was used in the other Examples set forth in the specification. This is longer than

the claimed hexamer. The specification gives a list of nucleic acids sequences that could be used in the claimed invention (see Tables 4 and 5). However, they comprise more than 6 (hexamer) nucleotides. Further, the specification at [0180] states that "[I]t is *predicted* that additional IMS oligonucleotides will have similar or improved efficacy in altering the course of autoimmune disease. The sequence of these additional IMS oligonucleotides are based on the efficacy data obtained with the IMS oligonucleotide described earlier." (see [0180]-[0181])

The state of the art is unpredictable with regard to the use of oligo-nucleotides of less than 8 nucleotides having immunostimulatory activity and with regard to the minimum length of the oligonucleotide. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract). Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 1 14, bottom

of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT" (p. 115). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans. Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility,. ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618). Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage. Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although "ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN." (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2).

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a composition comprising an oligonucleotides of *any* size, which is claimed. One skilled in the art would not accept on its face the examples using one IMS given in the specification as being representative of claimed composition in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms to determine if the claimed composition is immune modulatory (i.e. immuno-stimulatory or suppressive). Since the specification fails to provide particular guidance with regard to the scope of the claimed invention (any size CpG or variant being immunostimulatory or suppressive) is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

With respect to linkage modifications, combinations thereof or ribose nucleotides or combinations with deoxynucleotides and complexed or linked to biodegradable carriers; Weiner (J. Leukocyte Biology, 68:456-463, 2000) states that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see page 461). While the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, the

incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agarwal et al, Molecular Med, Today, 6:72-81, 2000, especially pp 78-80). Further, the state of the art teaches that the phosphorothioate analogs are the most potent in immune stimulation (see Zhao et al (Biochemical Pharmacology, 51:173-182, 1996, page 173 (abstract) and there is no evidence of record that any sequence that is not fully phosphorothiolated provides for immune stimulation in any model.

Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary

skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims is quite broad in view of the scope of the possible large number of oligonucleotides that can be used in the claimed composition. The nature of the invention and the state of the art has been described above. The level of one of ordinary skill is high (PhD level). The art is unpredictable as previously indicated. With regard to factors 6 and 7, the specification does not provide sufficient direction and the working examples do not enable the broad scope of the claimed oligonucleotides used in the instantly claimed composition. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled. For reasons stated above (i.e. lack of enabling disclosure, unpredictability of the art, lack of guidance) it would require undue experimentation to practice the claimed invention.

6. Claims 7-10 and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims (independent claim 7) is directed to a nucleic acid composition comprising: a nucleic acid vector having at least one cytosine to non-cytosine substitution within a CpG motif, wherein the CpG motif is of the formula 5'-purine-pyrimidine-C-G- pyrimidine-pyrimidine-3' or 5'-purine-purine-C-G-pyrimidine-pyrimidine-3', and wherein the cytosine to non-cytosine substitution is within the CpG dinucleotide.

The claims are drawn to a vast genus of oligonucleotides (CpG motifs and variants having the hexamer). To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of oligonucleotides, Applicant must adequately describe the function for the composition comprising the nucleic acid vector having the CpG motif with hexamer. The claims do not define a function for the oligonucleotides.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of oligonucleotides to which the claims are drawn, such as a correlation between the structure and function so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of oligonucleotides. Applicants have given a list of possible oligonucleotides (Table 4 and 5) however, the specification also states that "[I]t is *predicted* that additional IMS oligonucleotides will have similar or improved efficacy in altering the course of autoimmune disease. The sequence of these additional IMS oligonucleotides are based on the efficacy data obtained with the IMS oligonucleotide described earlier." (see [0180]-[0181])

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d

1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 7-9 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin-Orozco et al (International Immunology, 1999, 11/7:1111-1118).

Martin-Orozco et al discloses compositions comprising plasmid DNA (i.e. vector) having synthetic oligonucleotides (abstract; materials and methods). Martin-Orozco et al discloses an oligonucleotide comprising a hexamer ACGTTC (i.e. 5'-purine-pyrimidine-C-G-pyrimidine-pyrimidine-3'). The prior art discloses a plasmid pUC19, bacterial plasmid containing the oligonucleotide (p. 1112, material and methods). The prior art anticipates the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' compositions with the compositions of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed compositions and the

compositions of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

10. Claims 7-10, 25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Raz et al (6225292; issued May 1, 2001) or under 35 U.S.C. 102(e) as being anticipated by Carson et al (6610661).

Raz et al, for example, discloses a nucleic acid composition comprising a nucleic acid vector (i.e. recombinant expression vector) comprising having oligonucleotides (abstract; claims). Raz et al discloses an oligonucleotide comprising a hexamer (i.e. 5'-purine-pyrimidine-C-G-pyrimidine-pyrimidine-3' or 5'-purine-purine-C-G-pyrimidine-pyrimidine-3') (col. 2; col. 7; claims). The prior art anticipates the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' compositions with the compositions of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed compositions and the compositions of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

11. Claims 7 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipford et al (Immunology, 2000, 101:46-52).

Lipford et al discloses a nucleic acid composition comprising a vector (i.e. plasmid) having oligonucleotides (abstract; materials and methods). Lipford et al discloses the various hexamer regions (i.e. 5'-purine-pyrimidine-C-G-pyrimidine-pyrimidine-3' or 5'-purine-purine-C-G-pyrimidine-pyrimidine-3') (see Table 1, p.

47). The prior art discloses a hexamer having ACGTTC (i.e. 5'-purine-pyrimidine-C-G-pyrimidine-pyrimidine-3'; see 1668). Lipford et al discloses a hexamer GAGCTT (i.e. 5'-purine-purine-C-G-pyrimidine-pyrimidine-3'; see 1668-GC). Lipford et al discloses oligonucleotides having poly G regions at the 5' and 3' ends of the oligonucleotides (see Table 1). The prior art anticipates the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' compositions with the compositions of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed compositions and the compositions of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

12. No claims are allowed.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
September 28, 2007